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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Stace Lindsay et al.	Confirmation No.:	8638
Serial No.:	10/030,351	Art Unit:	1632
Filed:	June 7, 2002	Examiner:	Valarie E. Bertoglio
Customer No.:	21559		
Title:	EXPRESSION OF SECRETED HUMAN ALPHA-FETOPROTEIN IN TRANSGENIC ANIMALS		

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants request review of the final rejection in the above-identified application. No amendments are being filed with this request. This request is being filed with a Notice of Appeal.

The review is requested for the reasons stated on the attached sheets.

REMARKS

The Office rejects claims 1, 6, 7, and 21-24 as obvious over DeBoer (U.S. Patent No. 5,633,076; hereinafter "DeBoer"), Clark (U.S. Patent No. 5,32,775; hereinafter "Clark"), or Lubon (U.S. Patent No. 5,831,141; hereinafter "Lubon") in view of Morinaga et al. (PNAS 80:4604-4608; 1983; hereinafter "Morinaga") and Bennett (Breast Cancer Res. Treatment 45:169-179, 1997; hereinafter "Bennett") (Final Office Action, January 30, 2007; hereinafter "FA"). The Office states:

> Each of DeBoer, Clark and Lubon taught making transgenic mammals that produce and secrete a recombinant protein of interest into the milk of said mammal. As set forth in the rejection of record, the vast array of mammals used and proteins produced by said mammals renders obvious the method of making a mammal to express any protein of interest and to collect it in the milk given that Morinaga provided the additional teachings and motivation to apply the methods of each of DeBoer, Clark and Lubon to produce rHuAFP in the milk of mammals. Each of DeBoer, Clark and Lubon taught collecting and purifying their respective recombinant proteins, rendering it obvious to do so to rHuAFP as well. (FA, p. 3.)

Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, the Patent Office bears the burden of demonstrating that (1) there is some suggestion or motivation in the prior art to modify or combine the prior art teachings to obtain the claimed invention, (2) the prior art indicates that there is a reasonable expectation of success, and (3) the prior art reference(s) teach or suggest all of the claim limitations. See M.P.E.P. §§ 2142 and 2143. In the present case, as detailed below, Applicants submit that the Office has failed to establish a motivation to combine the prior art teachings and, therefore, a *prima facie* case of obviousness has not been established.

As the Federal Circuit has observed (emphasis added):

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is *casting the mind back to the time of invention*, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. . . . *Most if not all inventions arise from a combination of old elements*. . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention . . . Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or

> teaching of the desirability of making the specific combination that was made by the applicant.

In re Kotzab, 217 F.3d 1365, 1369-70, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000) (citations omitted) (emphasis added).

Moreover, the evidence of a suggestion, teaching, or motivation to combine "must be clear and particular." *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999), *abrogated on other grounds by In re Gartside*, 203 F.3d 1305, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). Applicant submits that, in the present case, the cited art fails to provide a clear and particular suggestion, teaching, or motivation to combine the references in such a way as to arrive at the claimed invention.

Present claims 1, 6, 7, and 21-24 are directed to a substantially pure nucleic acid molecule that includes: (i) a nucleic acid sequence encoding recombinant human alpha-fetoprotein (rHuAFP), (ii) a milk-specific promoter that is operably linked to the rHuAFP-encoding sequence, and (iii) a leader sequence encoding a protein secretory signal that enables secretion of rHuAFP by milk-producing cells into the milk of a mammal (Claim 1), a non-human transgenic mammal (e.g., a goat, cow, sheep, or pig) having the nucleic acid molecule described above as a transgene that is inserted into the genome of the mammal, which promotes expression of rHuAFP in mammary epithelial cells of the mammal (Claims 21 and 22), a method of preparing rHuAFP from the milk of the transgenic mammal described above (Claims 23 and 24), and milk from the non-human mammal described above that contains rHuAFP (Claims 6 and 7). The Office admits that none of DeBoer, Clark, or Lubon teaches each and every limitation of the instant claims. In particular, the Office states that "[t]he only elements lacking from...[DeBoer, Clark, and Lubon], alone or in combination, is the sequence encoding AFP and motivation to use the sequence in the techniques of any of DeBoer, Clark or Lubon" (see pp. 6-7 of Office Action dated October 31, 2005; emphasis added). Therefore, to remedy the deficiencies of DeBoer, Clark, and Lubon, the Office cites Morinaga and Bennett, stating that "Morinaga provided the additional teachings and motivation to apply the methods of each of DeBoer, Clark and Lubon to produce rHuAFP in the milk of mammals," while "Bennett supports a motivation to make recombinant AFP...[and] merely exemplifies the interest in producing large quantities of AFP"

(FA, pp. 3 and 4, respectively).

The Office has provided no evidence of any motivation, suggestion or teaching found in Morinaga or Bennett of the desirability of expressing rHuAFP in the milk of a transgenic mammal according to the techniques disclosed in DeBoer, Clark, or Lubon, as is required (see, e.g., *In re Kotzab*, *supra*). As was discussed on pp. 13-15 of the Reply to Office Action filed on September 22, 2005, Morinaga merely discloses the nucleic acid and predicted amino acid sequence of human AFP; it does not suggest the expression of rHuAFP in any context, much less in the milk of a transgenic non-human mammal under the control of a milk-specific promoter. Bennett only discloses the desirability of producing rHuAFP in *E. coli*, which is a non-mammalian expression system (see, e.g., pp. 8-9 and 13 of the Reply to Office Action dated November 22, 2006). Thus, both references fail to provide any motivation, suggestion or teaching to express rHuAFP in the milk of a transgenic mammal, and the Office has provided no evidence to the contrary.

The Office, though, states that because each of DeBoer, Clark and Lubon discloses the production of any protein of interest using any mammal, all that Morinaga and Bennett need to provide is rHuAFP as a protein of interest. This rationale impermissibly sidesteps the Office's required burden, when establishing a *prima facie* case of obviousness, of showing that the references provide a clear and particular motivation, suggestion, or teaching of the desirability of combining reference teachings to arrive at the invention recited in the rejected claims (*see, e.g., In re Kotzab*, *supra*, and *In re Dembiczak*, *supra*). Thus, the Office seeks to have it both ways, stating, absent any evidence to support the assertion in the references themselves, that Morinaga and Bennett provide motivation to combine their disclosures with those of DeBoer, Clark, or Lubon, while also stating that motivation is not required because the references are only relied upon for their disclosure of rHuAFP as a protein of interest. This double standard does not comport with the Federal Circuit's holdings in *In re Kotzab* and *In re Dembiczak*, described above, which clearly require that the cited references provide a "clear and particular" motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the present Applicants. The Office's lack of evidence supporting a motivation to combine references teachings is clear error.

Moreover, the fact that Applicants' claimed species of transgenic mammal may be encompassed by the generic genus disclosed by DeBoer, Clark, or Lubon does not by itself render Applicants' species obvious, especially given the lack of any motivation, suggestion, or teaching in Morinaga and Bennett to produce Applicants' rHuAFP-expressing transgenic mammal, as is discussed above and as was discussed in the Reply to Office Action dated November 22, 2006 (see, e.g., pp. 12-14; *see also In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)). The M.P.E.P. § 2144.08 (II)(A) states that to establish a *prima facie* case of obviousness in a genus-species situation it is essential that the Examiner find some motivation or suggestion to make the claimed invention in light of the prior art teachings. The Office states that, given DeBoer, Clark, or Lubon, Morinaga and Bennett provide the requisite motivation to produce Applicants' claimed transgenic mammal based solely on the fact that these references identify rHuAFP as a protein of interest. This determination is in error.

The mere possibility that a skilled artisan would have produced a transgenic mammal capable of expressing and secreting rHuAFP into its milk based solely on the knowledge of rHuAFP as a protein of interest (and without any deference to evidence in the prior art of a clear preference for expressing rHuAFP in a non-mammalian system) does not make the invention recited in present claims 1, 6, 7, and 21-24 obvious "'unless the prior art suggested the desirability of [such a] modification' or replacement" (see M.P.E.P. § 2144.08 (II)(A), quoting *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984)); *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). In this case, the Office has provided no evidence of any such motivation, suggestion, or teaching in Morinaga or Bennett suggesting the desirability of replacing the recombinant proteins identified in DeBoer, Clark, or Lubon with rHuAFP to produce a transgenic mammal capable of expressing rHuAFP in its milk. Rather, the Office has disregarded the fact that Morinaga provides no evidence at all to express HuAFP recombinantly and clear evidence in Bennett for expressing rHuAFP in bacteria only. Thus, as a matter of law, the combination of DeBoer, Clark, or Lubon with Morinaga and Bennett fails to establish a *prima facie* case of obviousness against present claims 1, 6, 7, and 21-24.

Finally, Applicants maintain that the Office has simply engaged in impermissible hindsight analysis to establish a basis for rejecting claims 1, 6-7, and 21-24 for obviousness.

Applicants have consistently emphasized that the case law makes clear that to avoid a hindsight-based obviousness analysis the Patent Office bears the burden of elucidating factual teachings, suggestions, or incentives in the prior art that would provide motivation to combine the cited references. *See, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 18, 148 U.S.P.Q. 459, 467 (1966) ("strict observance" of factual predicates to obviousness conclusion required), and M.P.E.P. § 2142. In this case, the Office has combined DeBoer, Clark, or Lubon with Morinaga and Bennett without evidence of any suggestion, teaching, or motivation to do so; the Examiner has simply taken Applicants' disclosure as a blueprint for piecing together the prior art to defeat patentability (*see, e.g., In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). This is clearly impermissible and is grounds for withdrawal of the rejection of claims 1, 6, 7, and 21-24 for obviousness.

For all of the reasons discussed above, Applicants respectfully request that the rejection of claims 1, 6, 7, and 21-24 under 35 U.S.C. § 103(a) for obviousness over DeBoer, Clark, or Lubon in view of Morinaga and Bennett should be withdrawn.

CONCLUSION

Applicants submit that present claims 1, 6, 7, and 21-24 are in condition for allowance, and such action is respectfully requested.

If there are any other charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Date: 30 April 2007

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